# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>GRF/BP6215651 | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No.<br>PCT/GB2004/001495 | International filing date *(day/month/year)*<br>05.04.2004 | Priority date *(day/month/year)*<br>05.04.2003 |
| International Patent Classification (IPC) or national classification and IPC<br>G01N33/50 | | |
| Applicant<br>THE UNIVERSITY COURT OF THE UNIV. OF GLASGOW et al | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☐ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 28.01.2005 | 21.06.2005 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized Officer<br>Schalich, J<br>Telephone No. +49 89 2399-8915 |

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)**

International application No.
PCT/GB2004/001495

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

D1: MILLER FRED R ET AL: "Growth Factors in Mouse Mammary Cell Interactions in Vitro" ANTICANCER RESEARCH, vol. 14, no. 5A, 1994, pages 2033-2038

D2: DELVENNE P ET AL: "The organotypic culture of HPV-transformed keratinocytes: an effective in vitro model for the development of new immunotherapeutic approaches for mucosal (pre)neoplastic lesions" VACCINE, BUTTERWORTH SCIENTIFIC. GUILDFORD, GB, vol. 19, no. 17-19, 21 March 2001 (2001-03-21), pages 2557-2564

D3: HASSAN RAFFIT ET AL: "Antitumor activity of SS(dsFv)PE38 and SS1(dsFv)PE38, recombinant antimesothelin immunotoxins against human gynecologic cancers grown in organotypic culture in vitro." CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH. NOV 2002, vol. 8, no. 11, November 2002 (2002-11), pages 3520-3526

D4: EICHER S A ET AL: "Evaluation of topical gene therapy for head and neck squamous cell carcinoma in an organotypic model." CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH. OCT 1996, vol. 2, no. 10, October 1996 (1996-10), pages 1659-1664

D5: WO 03/018752 A (WISTAR INST ; HERLYN MEENHARD (US); KALABIS JIRI (US)) 6 March 2003 (2003-03-06)

**1. Art. 33(2) PCT**

The subject-matter of **claims 1-16** is new in the sense of Article 33(2) PCT.

**2. Art. 33(3) PCT**

The present application does not meet the criteria of Article 33(1) PCT, because the

subject-matter of **claims 1-16** does not involve an inventive step in the sense of Article 33(3) PCT.

Organotypic (raft) cell culture models for testing agents for their effect on a variety of different cell types are well known in the art.
Documents D2-D5 disclose organotypic cultures consisting of fibroblasts grown in collagen gels and different cancers cells grown on top or within these matrices. Said models are used for evaluating the (therapeutic) effect of different agents.
Contrary to the argument of the Applicant, that the tissue models described in the prior art only utilise tumour cells at a single stage of tumourigenesis , D2 (par 2.2 and p 2562, co 1, par 3 until p 2563, co 1, par 1) uses tumour cells at different stages of tumourigenesis for organotypic cultures, which are further tested for the effect of a test agent, as described in present claim 1: EIL8 (non-tumourigenic), 18-11S3 (tumourigenic after 60 passages in tissue culture) and SiHa, CasKi, C4-II (all tumourigenic).
The subject-matter of claim 1 differs from these known models in that cells from a different host are used.
The problem to be solved by the present invention may therefore be regarded as providing a murine organotypic culture model for testing agents.
The solution, to use murine cells instead of human cells can however not be considered as involving an inventive step (Article 33(3) PCT), since the use of murine cells, if a murine tumour model is to be investigated, is obvious, does not pose any problems and is routine practice in the art (D1).

Dependent claims 2-15 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step since the corresponding subject-matter is either disclosed in documents D2-D5 or routine practice in the art.

**3. Art. 33(4) PCT**

**Claims 1-15** are industrially applicable.

**Re Item VIII**

**Certain observations on the international application**

**Art. 6 PCT**

The arguments of the Applicant were taken into account.

1. The use of the terms "model" and "tissue model" in **claim 1** leads to a lack of clarity as the terms appear to be used interchangeably.

2. The terms "observing an effect" and "observing the effect" used in **claim 1** and claim 1e) are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter and the scope of said claim unclear, Article 6 PCT.

3. In view of the definition of the model found at page 10, par 1, the embodiments described in claim 9 and 10 seem to contradict claim 1, especially step a), which adds to the confusion as to the precise scope of the **claims 1, 10 and 11**.

CLAIMS:

1. An *in vitro* method for observing an effect of a test agent on a model of a murine tumour, wherein the model represents the progression from normal tissue to benign tumour tissue, and from benign tumour tissue to malignant tumour tissue, the method comprising the steps of:

a) providing a first synthetic murine living tissue model comprising a three-dimensional array of murine fibroblasts in a collagen gel and at least a first murine test cell, wherein the first test cell is a model of normal tissue;

b) providing a second synthetic murine living tissue model comprising a three-dimensional array of murine fibroblasts in a collagen gel and at least a second murine test cell, wherein the second test cell is a model of benign tumour tissue;

c) providing a third synthetic murine living tissue model comprising a three-dimensional array of murine fibroblasts in a collagen gel and at least a third murine test cell, wherein the third test cell is a model of malignant tumour tissue;

d) contacting the test agent with said living tissue models; and

e) observing the effect the test agent has on said test cells.

2. A method according to claim 1 wherein each model comprises a test cell supported on a surface of the array.

3. A method according to claim 2 wherein each model comprises a plurality of test cells which form a layer supported on a surface of the array.

4. A method according to claim 1 wherein each model comprises a test cell located within the array.

5. A method according to any one of claims 1 to 4 wherein the fibroblasts and test cells are derived from the same tissue type.

6. A method according to any one of claims 1 to 5 wherein the test cells are epithelial cells.

7. A method according to claim 6 wherein the test cells are from skin, mammary, lung, or intestinal epithelium.

8. A method according to claim 7 wherein the second murine test cell is an SP-1 cell and the third murine test cell is a T52 Hufos cell.

9. A method according to claim 8 wherein the first murine test cell is a BalbMK cell.

10. A method according to any one of claims 1 to 9 wherein the second model comprises a normal test cell and a benign tumour test cell.

11. A method according to any one of claims 1 to 10 wherein the third model comprises a normal test cell and a malignant tumour test cell.

12. A method according to any one of the preceding claims wherein the test cells are labelled.

13. A method according to any one of the preceding claims wherein the test agent is a chemical agent, pharmaceutical, peptide, protein or nucleic acid or radiation.

14. A method according to any one of claims 1 to 12 wherein the test agent is a delivery vehicle for a therapeutic agent.

15. A method according to any one of the preceding claims comprising determining the effect of the test agent on test cell number, area, volume, shape, morphology, marker expression or chromosomal fragmentation.

16. A method according to any one of the preceding claims further comprising the step of selecting an agent which has a desired effect on the test cell.